

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	350	(dipeptidyl adj peptidase adj IV) or (DP adj IV)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:35			0
2	BRS	L2	211	1 same inhibit\$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:36			0
3	BRS	L3	7	2 same (unstable or masked)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:37			0
4	BRS	L4	3	(Ile-thia) or (ile-pyr) or (val-thia) or (val-pyr)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:48			0
5	BRS	L5	1	(dipeptidyl adj alkyl adj ketone) or (dipeptidyl adj fluoroalkyl adj ketone) or (dipeptidyl adj chloroalkyl adj ketone) or (dipeptidyl adj cyanide) or (dipeptidyl adj pyridium adj methyl adj ketone)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:50			0
6	BRS	L6	815660	acetate or succinate or tartrate or fumarate or phosphate or sulfate	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:52			0
7	BRS	L7	0	3 same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:52			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Error Rows
8	BRS	L8	45472	(metabolic adj disorder) or diabetes or (impaired adj glucose adj tolerance) or (diabetic adj neuropathy) or nephropathy	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:55			0
9	BRS	L9	2	3 same 8	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/16 19:55			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L7	7	((((dipeptidyl adj peptidase adj IV) or (DP adj IV) ) same inhibit3 ) same (unstable or masked)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:36			0
2	BRS	L8	3040	(alkyl adj ketone) or (fluoroalkyl adj ketone) or (chloroalkyl adj ketone) or (peptide adj cyanide) or (pyridium adj methyl adj ketone)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:37			0
3	BRS	L9	211	((dipeptidyl adj peptidase adj IV) or (DP adj IV) ) same inhibit3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:38			0
4	BRS	L10	2	8 same 9	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:45			0
5	BRS	L11	27	demuth adj hans-ulrich.in..	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:46			0
6	BRS	L12	0	schmidt adj jorn.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:46			0
7	BRS	L13	40	hoffmann adj torsten.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:47			0
8	BRS	L14	13	glund adj konrad.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:47			0
9	BRS	L15	3	(7 or 10) and (11 or 13 or 14)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/01/1 7 09:48			0

FILE 'HOME' ENTERED AT 19:59:44 ON JAN 2003

=> file medline caplus biosis embase scisearch agricola

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'MEDLINE' ENTERED AT 20:00:10 ON 16 JAN 2003

FILE 'CAPLUS' ENTERED AT 20:00:10 ON 16 JAN 2003

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FILE 'EMBASE' ENTERED AT 20:00:10 ON 16 JAN 2003

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FILE 'SCISEARCH' ENTERED AT 20:00:10 ON 16 JAN 2003

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FILE 'AGRICOLA' ENTERED AT 20:00:10 ON 16 JAN 2003

=> s (dipeptidyl peptidase IV) or (dp IV)

L1 5816 (DIPEPTIDYL PEPTIDASE IV) OR (DP IV)

=> s l1 (p) inhibit?

L2 1726 L1 (P) INHIBIT?

=> s l2 (p) (unstable or masked)

L3 14 L2 (P) (UNSTABLE OR MASKED)

=> duplicate remove l3

DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'

KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n

PROCESSING COMPLETED FOR L3

L4 5 DUPLICATE REMOVE L3 (9 DUPLICATES REMOVED)

=> d l4 1-5 ibib abs

L4 ANSWER 1 OF 5

MEDLINE

DUPLICATE 1

ACCESSION NUMBER: 2001410442 MEDLINE

DOCUMENT NUMBER: 21235368 PubMed ID: 11337057

TITLE: Transbuccal peptide delivery: stability and in vitro permeation studies on endomorphin-1.

AUTHOR: Bird A P; Faltinek J R; Shojaei A H

CORPORATE SOURCE: Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, TX 79106, USA.

SOURCE: JOURNAL OF CONTROLLED RELEASE, (2001 May 18) 73 (1) 31-6.

Journal code: 8607908. ISSN: 0168-3659.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200107

ENTRY DATE: Entered STN: 20010723

Last Updated on STN: 20010723

Entered Medline: 20010719

AB The purpose of this study was to investigate the feasibility of buccal delivery of a model peptide, endomorphin-1 (ENI), using stability and in vitro permeation studies. ENI is a recently isolated mu-opiate receptor agonist with high selectivity and specificity for this receptor subtype. Stability studies were conducted in various buffers and the drug was shown to be stable in both acidic and basic buffer systems. In the presence of full thickness porcine buccal epithelium, ENI was \*\*\*unstable\*\*\* with only 23.4+/-15.7% intact drug present after 6 h. The region responsible for this degradation was found to coincide with the major barrier region of the buccal epithelium as delineated through stability experiments in

the presence of partial thickness buccal epithelium. Various pentidase  
 \*\*\*inhibitors\*\*\* were used to isolate the enzyme(s) responsible for this  
 degradation. Diprotin-A, a potent \*\*\*inhibitor\*\*\* of  
 \*\*\*dipeptidyl\*\*\* \*\*\*peptidase\*\*\* \*\*\*IV\*\*\*, provided significant  
 \*\*\*inhibition\*\*\* of the degradation of ENI in the presence of buccal  
 epithelium. In vitro permeation studies revealed that the permeability  
 coefficient of ENI across porcine buccal epithelium was  $5.67 \pm 4.74 \times 10^{-7}$   
 cm/s. The enzymatic degradation of ENI was found not to be rate limiting  
 to the drug's permeation across buccal epithelium, as diprotin-A did not  
 increase the permeation of ENI. Sodium glycocholate as well as sodium  
 taurocholate were also ineffective in enhancing the permeation of ENI  
 across porcine buccal epithelium.

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:819402 CAPLUS

DOCUMENT NUMBER: 132:36038

TITLE: Synthesis of prodrugs of \*\*\*unstable\*\*\*

\*\*\*dipeptidyl\*\*\* \*\*\*peptidase\*\*\* \*\*\*IV\*\*\*

\*\*\*inhibitors\*\*\* for use in treating diabetes

INVENTOR(S): Demuth, Hans-Ulrich; Schmidt, Jorn; Hoffmann, Torsten;

Glund, Konrad

PATENT ASSIGNEE(S): Probiodrug Gesellschaft Fur Arzneimittelforschung

m.b.H., Germany

SOURCE: PCT Int. Appl., 41 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967279	A1	19991229	WO 1999-EP4381	19990624
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
DE 19828114	A1	20000127	DE 1998-19828114	19980624
CA 2335978	AA	19991229	CA 1999-2335978	19990624
AU 9947772	A1	20000110	AU 1999-47772	19990624
BR 9911415	A	20010320	BR 1999-11415	19990624
EP 1090030	A1	20010411	EP 1999-931163	19990624
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2002518518	T2	20020625	JP 2000-555930	19990624
NO 2000006483	A	20001219	NO 2000-6483	20001219
US 2001020006	A1	20010906	US 2000-745883	20001221
PRIORITY APPLN. INFO.:			DE 1998-19828114 A	19980624
			WO 1999-EP4381 W	19990624

OTHER SOURCE(S): MARPAT 132:36038

GI

/ Structure 1 in file .gra /

AB The invention relates to compds. of \*\*\*unstable\*\*\* \*\*\*inhibitors\*\*\*  
 of \*\*\*dipeptidyl\*\*\* \*\*\*peptidase\*\*\* \*\*\*IV\*\*\* ( \*\*\*DP\*\*\*  
 \*\*\*IV\*\*\* ) which comprise general formula A-B-C, whereby A represents an  
 amino acid, B represents the chem. bond between A and C or an amino acid,  
 and C represents an \*\*\*unstable\*\*\* \*\*\*inhibitor\*\*\* of \*\*\*DP\*\*\*  
 \*\*\*IV\*\*\*. Such compds. are used for treating altered glucose tolerance,  
 glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus,  
 diabetic neuropathy, nephropathy, and secondary diseases in mammals caused  
 by diabetes mellitus. Thus, (I) was reacted with pyridine to give [(II);  
 R = Cbz], which was deprotected to give II (R = H) (III) which is thought  
 to undergo an intramol. cyclization (no data) to form the active

\*\*\*DP\*\*\*      \*\*\*IV\*\*\*      \*\*\*inhibitor\*\*\*      . In 0.1 M HEPES-buffer, pH 7.6, at 25.degree., III had a half life (before self-cyclization) of 13.3 min.

REFERENCE COUNT:                      4      THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4      ANSWER 3 OF 5      MEDLINE      DUPLICATE 2  
ACCESSION NUMBER:      1998327123      MEDLINE  
DOCUMENT NUMBER:      98327123      PubMed ID: 9660870  
TITLE:      Functional specialization of stable and dynamic microtubules in protein traffic in WIF-B cells.  
AUTHOR:      Pous C; Chabin K; Drechou A; Barbot L; Phung-Koskas T; Settegrana C; Bourguet-Kondracki M L; Maurice M; Cassio D; Guyot M; Durand G  
CORPORATE SOURCE:      Laboratoire de Biochimie Generale, Equipe d'Accueil 1595, Unite de Formation et de Recherche de Pharmacie, Universite Paris-Sud, 92296 Chatenay-Malabry, France.  
SOURCE:      JOURNAL OF CELL BIOLOGY, (1998 Jul 13) 142 (1) 153-65.  
Journal code: 0375356. ISSN: 0021-9525.  
PUB. COUNTRY:      United States  
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE:      English  
FILE SEGMENT:      Priority Journals  
ENTRY MONTH:      199808  
ENTRY DATE:      Entered STN: 19980828  
Last Updated on STN: 19980828  
Entered Medline: 19980820

AB      We found that the magnesium salt of ilimaquinone, named 201-F, specifically disassembled dynamically \*\*\*unstable\*\*\* microtubules in fibroblasts and various epithelial cell lines. Unlike classical tubulin-interacting drugs such as nocodazole or colchicine which affect all classes of microtubules, 201-F did not depolymerize stable microtubules. In WIF-B-polarized hepatic cells, 201-F disrupted the Golgi complex and \*\*\*inhibited\*\*\* albumin and alpha1-antitrypsin secretion to the same extent as nocodazole. By contrast, 201-F did not impair the transport of membrane proteins to the basolateral surface, which was only affected by the total disassembly of cellular microtubules. Transcytosis of two apical membrane proteins-the alkaline phosphodiesterase B10 and \*\*\*dipeptidyl\*\*\* \*\*\*peptidase\*\*\* \*\*\*IV\*\*\* -was affected to the same extent by 201-F and nocodazole. Taken together, these results indicate that only dynamically \*\*\*unstable\*\*\* microtubules are involved in the transport of secretory proteins to the plasma membrane, and in the transcytosis of membrane proteins to the apical surface. By contrast, stable microtubules, which are not functionally affected by 201-F treatment, are involved in the transport of membrane proteins to the basolateral surface. By specifically disassembling highly dynamic microtubules, 201-F is an invaluable tool with which to study the functional specialization of stable and dynamic microtubules in living cells.

L4      ANSWER 4 OF 5      EMBASE      COPYRIGHT 2003 ELSEVIER SCI. B.V.  
ACCESSION NUMBER:      95220827      EMBASE  
DOCUMENT NUMBER:      1995220827  
TITLE:      Amino acid and peptide phosphonate derivatives as specific inhibitors of serine peptidases.  
AUTHOR:      Oleksyszyn J.; Powers J.C.  
CORPORATE SOURCE:      OsteoArthritis Sciences, Inc., Cambridge, MA 02139, United States  
SOURCE:      Methods in Enzymology, (1994) 244/- (423-441).  
ISSN: 0076-6879      CODEN: MENZAU  
COUNTRY:      United States  
DOCUMENT TYPE:      Journal; Article  
FILE SEGMENT:      029      Clinical Biochemistry  
LANGUAGE:      English  
SUMMARY LANGUAGE:      English

AB      Peptidyl derivatives of .alpha.-aminoalkyl phosphonate diphenyl esters have a number of advantages for in vitro and in vivo experiments compared to other commonly used peptide serine peptidase \*\*\*inhibitors\*\*\* . They are easily synthesized, are chemically very stable, and are not alkylating agents such as the commonly used peptide chloromethyl ketone serine peptidase \*\*\*inhibitors\*\*\* . They are more stable than most other organophosphorus \*\*\*inhibitors\*\*\* , including peptidyl derivatives of

the .alpha.-aminoalkyl phosphonates, where the phosphonate moiety is chemically activated by the presence of better leaving groups. .alpha.-aminoalkyl phosphonate diphenyl esters have outstanding stability (t(1/2) usually greater than 4 days at pH 7.5; >24 hr in plasma). Thus, low \*\*\*inhibitor\*\*\* concentrations can effectively control unwanted serine peptidase activity with low \*\*\*inhibitor\*\*\* concentrations over long time periods, which makes them perfect tools for experiments involving cells. Because .alpha.-aminoalkyl phosphonate diphenyl esters are irreversible \*\*\*inhibitors\*\*\*, they offer real advantages in many experimental situations over reversible \*\*\*inhibitors\*\*\* in cases in which it may be necessary to maintain high concentrations of the reversible \*\*\*inhibitor\*\*\* for long time periods. The second-order \*\*\*inhibition\*\*\* rate constants for phosphonate \*\*\*inhibitors\*\*\* are usually not as high as those observed with other types of peptidyl serine peptidase \*\*\*inhibitors\*\*\*. This is compensated for by their high stability and specificity. The irreversible character of the \*\*\*inhibition\*\*\* reaction allows effective \*\*\*inhibition\*\*\* even if the inactivation rate constant is not large. For example, Cbz-Val(P)(OPh)<sub>2</sub> \*\*\*inhibits\*\*\* HLE with a rate constant of 260 M<sup>-1</sup> sec<sup>-1</sup>. Thus at an effective concentration of 10 .mu.M, 50% of the enzyme is inactivated after 4.5 min, and almost no activity is detected after an 11-min incubation time. Frequently there is a need to specifically \*\*\*inhibit\*\*\* serine peptidases in vitro during protein purification procedures or in biological experiments involving cells or tissue culture. Typically, peptide chloromethyl ketone derivatives are used. However, these inactivators are quite nonspecific alkylating agents and experimental results can be misleading. For example, the presence of a chymotrypsin-like enzyme activity on the neutrophil membrane was assumed when \*\*\*inhibition\*\*\* with Tos-Phe-CH<sub>2</sub>Cl resulted in \*\*\*inhibition\*\*\* of the so-called oxidative burst of these cells. However, it has been shown that the targeted protein is not a serine peptidase, and \*\*\*inhibition\*\*\* results from a nonspecific alkylation reaction. As another example of the utility of phosphonates, dipeptide derivatives of .alpha.-aminoalkyl phosphonate diphenyl ester derivatives with a P1 proline residue are effective \*\*\*inhibitors\*\*\* for \*\*\*dipeptidyl\*\*\* - \*\*\*peptidase\*\*\* \*\*\*IV\*\*\*. The corresponding dipeptide boronic acid and chloromethyl ketone derivatives are \*\*\*unstable\*\*\*. In summary, peptidyl derivatives of .alpha.-aminoalkyl phosphonate diphenyl esters are highly specific irreversible \*\*\*inhibitors\*\*\* of serine peptidases and are chemically stable and stable in plasma. They offer a number of advantages over other types of \*\*\*inhibitors\*\*\* currently in use in biological experiments. After reaction with the enzyme, they form very stable enzyme- \*\*\*inhibitor\*\*\* complexes, making them interesting tools for X-ray studies on the active site structure of new serine peptidases.

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3  
 ACCESSION NUMBER: 1982:522831 CAPLUS  
 DOCUMENT NUMBER: 97:122831  
 TITLE: Dipeptidyl peptidase IV inhibits the polymerization of fibrin monomers  
 AUTHOR(S): Mentlein, Rolf; Heymann, Eberhard  
 CORPORATE SOURCE: Med. Fak., Univ. Kiel, Kiel, D-2300, Fed. Rep. Ger.  
 SOURCE: Archives of Biochemistry and Biophysics (1982), 217(2), 748-50  
 CODEN: ABBIA4; ISSN: 0003-9861  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB A highly purified \*\*\*dipeptidyl\*\*\* \*\*\*peptidase\*\*\* \*\*\*IV\*\*\* (I) from human placenta cleaved glycylproline from the N-terminal end of the fibrin .alpha. chain and \*\*\*inhibited\*\*\* the clotting of fibrin monomers. This result underlined the importance of the N-terminus of the fibrin .alpha. chain as an aggregation site \*\*\*masked\*\*\* by fibrinopeptide A. Apparently, I can hinder blood coagulation in intact vessels in vivo, because it is located on the surface of the capillary endothelium.

=> s (dipeptidyl alkyl ketone) or (dipeptidyl fluoroalkyl ketone) ot (dipeptidyl chloroalkyl keton MISSING OPERATOR KETONE) OT  
 The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s (dipeptidyl alkyl ketone)  
L5 0 (DIPEPTIDYL ALKYL KETONE)

=> s (dipeptidyl fluoroalkyl ketone) or (dipeptidyl chloroalkyl ketone) or (dipeptidyl cyanide) or  
L6 1 (DIPEPTIDYL FLUOROALKYL KETONE) OR (DIPEPTIDYL CHLOROALKYL KETON  
E) OR (DIPEPTIDYL CYANIDE) OR (DIPEPTIDYL PYRIDIDIUM METHYL KETONE  
)

=> d l6 1 ibib abs

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:142666 CAPLUS

DOCUMENT NUMBER: 136:200479

TITLE: Preparation of proline derivatives as dipeptidyl  
peptidase IV (DPP-IV) inhibitors and use thereof as  
drugs

INVENTOR(S): Kitajima, Hiroshi; Sakashita, Hiroshi; Akahoshi,  
Fumihiko; Hayashi, Yoshiharu

PATENT ASSIGNEE(S): Welfide Corporation, Japan

SOURCE: PCT Int. Appl., 340 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014271	A1	20020221	WO 2001-JP6906	20010810
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2001077754	A5	20020225	AU 2001-77754	20010810
PRIORITY APPLN. INFO.:			JP 2000-243217	A 20000810
			JP 2000-400296	A 20001228
			WO 2001-JP6906	W 20010810

OTHER SOURCE(S): MARPAT 136:200479

GI

/ Structure 2 in file .gra /

AB The title compds. [I; X = NR1R2, NR3COR4, NR5COR4, NR5CH2CH2NR6R7, NR8SO2R9, OR10, O2CR11; wherein R1, R2 = H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, or they are linked to each other to form a heterocyclyl contg. 1 or 2 N atoms or O which may be a spiro ring and is optionally fused to an (un)substituted arom. ring; R3, R4 = H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl; R5, R6, R7 = H, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, or which is optionally fused to an (un)substituted arom. ring; R8, R9, R10, R11 = H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl] or pharmacol. acceptable salts thereof are prepd. These compds. are useful for the treatment of DPP-IV related diseases such as diabetes, obesity, HIV infection, cancer metastasis, skin diseases, prostatic hypertrophy (prostatomegaly), pericementitis, or autoimmune diseases. Thus, a soln. of 0.924 g (S)-1-[(2S,4S)-4-amino-1-tert-butoxycarbonyl-2-pyrrolidinylcarbonyl]-2-cyanopyrrolidine (prepn. given), 1.7 mL diisopropylethylamine, and 0.78 g 2-chloro-4-fluorobenzonitrile in 10 mL N-methyl-2-pyrrolidone were stirred at 80.degree. for 4 h to give 0.94 g (S)-1-[(2S,4S)-1-tert-butoxycarbonyl-4-(3-chloro-4-cyanophenyl)amino-2-pyrrolidinylcarbonyl]-2-cyanopyrrolidine



which (0.93 g) was treated with HCl/EtOAc at room temp. for 15 h to give  
(S)-1-[(2S,4S)-4-(3-chloro-4-phenyl)amino-2-pyrrolidinyl]carbonyl]-2-  
cyanopyrrolidine hydrochloride (II). II showed IC50 of 0.13 and 0.15 nM  
against human blood plasma DPP-IV and rat blood plasma DPP-IV, resp.  
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 19:59:44 ON 16 JAN 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT  
20:00:10 ON 16 JAN 2003

L1 5816 S (DIPEPTIDYL PEPTIDASE IV) OR (DP IV)  
L2 1726 S L1 (P) INHIBIT?  
L3 14 S L2 (P) (UNSTABLE OR MASKED)  
L4 5 DUPLICATE REMOVE L3 (9 DUPLICATES REMOVED)  
L5 0 S (DIPEPTIDYL ALKYL KETONE)  
L6 1 S (DIPEPTIDYL FLUOROALKYL KETONE)OR (DIPEPTIDYL CHLOROALKYL KE

=> s acetate or succinate or tartrate or fumarate or phosphate or sulfate

5 FILES SEARCHED...

L7 2933765 ACETATE OR SUCCINATE OR TARTRATE OR FUMARATE OR PHOSPHATE OR  
SULFATE

=> s l7 (p0 l4

MISSING OPERATOR 'L43 (P0'

The search profile that was entered contains terms or  
nested terms that are not separated by a logical operator.

=> s l7 (p) l4

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L39 (P) L48'  
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L41 (P) L52'  
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L42 (P) L54'  
L8 0 L7 (P) L4

=> s (metabolic disorder) or diabetes or (impaired glucose tolerance) or (diabetic neuropathy) or

L9 790513 (METABOLIC DISORDER) OR DIABETES OR (IMPAIRED GLUCOSE TOLERANCE)  
OR (DIABETIC NEUROPATHY) OR NEPHROPATHY

=> d his

(FILE 'HOME' ENTERED AT 19:59:44 ON 16 JAN 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT  
20:00:10 ON 16 JAN 2003

L1 5816 S (DIPEPTIDYL PEPTIDASE IV) OR (DP IV)  
L2 1726 S L1 (P) INHIBIT?  
L3 14 S L2 (P) (UNSTABLE OR MASKED)  
L4 5 DUPLICATE REMOVE L3 (9 DUPLICATES REMOVED)  
L5 0 S (DIPEPTIDYL ALKYL KETONE)  
L6 1 S (DIPEPTIDYL FLUOROALKYL KETONE)OR (DIPEPTIDYL CHLOROALKYL KE  
L7 2933765 S ACETATE OR SUCCINATE OR TARTRATE OR FUMARATE OR PHOSPHATE OR  
L8 0 S L7 (P) L4  
L9 790513 S (METABOLIC DISORDER) OR DIABETES OR (IMPAIRED GLUCOSE TOLERAN

=> s l4 (p) l9

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L68 (P) L59'  
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L72 (P) L61'  
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH  
FIELD CODE - 'AND' OPERATOR ASSUMED 'L74 (P) L62'  
L10 1 L4 (P) L9

=> d l10 1 ibib abs

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:819402 CAPLUS  
 DOCUMENT NUMBER: 132:36038  
 TITLE: Synthesis of prodrugs of \*\*\*unstable\*\*\*  
           \*\*\*dipeptidyl\*\*\*        \*\*\*peptidase\*\*\*        \*\*\*IV\*\*\*  
           \*\*\*inhibitors\*\*\*       for use in treating  
           \*\*\*diabetes\*\*\*  
 INVENTOR(S): Demuth, Hans-Ulrich; Schmidt, Jorn; Hoffmann, Torsten;  
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WO 9967279	A1	19991229	WO 1999-EP4381	19990624
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG DE 19828114 A1 20000127 DE 1998-19828114 19980624 CA 2335978 AA 19991229 CA 1999-2335978 19990624 AU 9947772 A1 20000110 AU 1999-47772 19990624 BR 9911415 A 20010320 BR 1999-11415 19990624 EP 1090030 A1 20010411 EP 1999-931163 19990624 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO JP 2002518518 T2 20020625 JP 2000-555930 19990624 NO 2000006483 A 20001219 NO 2000-6483 20001219 US 2001020006 A1 20010906 US 2000-745883 20001221 PRIORITY APPLN. INFO.: DE 1998-19828114 A 19980624 WO 1999-EP4381 W 19990624				

OTHER SOURCE(S): MARPAT 132:36038  
 GI

/ Structure 3 in file .gra /

AB The invention relates to compds. of \*\*\*unstable\*\*\*        \*\*\*inhibitors\*\*\*  
 of \*\*\*dipeptidyl\*\*\*        \*\*\*peptidase\*\*\*        \*\*\*IV\*\*\* ( \*\*\*DP\*\*\*  
       \*\*\*IV\*\*\* ) which comprise general formula A-B-C, whereby A represents an  
 amino acid, B represents the chem. bond between A and C or an amino acid,  
 and C represents an \*\*\*unstable\*\*\*        \*\*\*inhibitor\*\*\* of \*\*\*DP\*\*\*  
       \*\*\*IV\*\*\* . Such compds. are used for treating altered glucose tolerance,  
 glucosuria, hyperlipidemia, metabolic acidosis, \*\*\*diabetes\*\*\*  
 mellitus, \*\*\*diabetic\*\*\*        \*\*\*neuropathy\*\*\* , \*\*\*nephropathy\*\*\* ,  
 and secondary diseases in mammals caused by \*\*\*diabetes\*\*\* mellitus.  
 Thus, (I) was reacted with pyridine to give [(II); R = Cbz], which was  
 deprotected to give II (R = H) (III) which is thought to undergo an  
 intramol. cyclization (no data) to form the active \*\*\*DP\*\*\*        \*\*\*IV\*\*\*  
       \*\*\*inhibitor\*\*\* . In 0.1 M HEPES-buffer, pH 7.6, at 25.degree., III had  
 a half life (before self-cyclization) of 13.3 min.

REFERENCE COUNT: 4        THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS  
                                   RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 19:59:44 ON 16 JAN 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT  
 20:00:10 ON 16 JAN 2003

L1 5816 S (DIPEPTIDYL PEPTIDASE IV) OR (DP IV)  
 L2 1726 S L1 (P) INHIBIT?  
 L3 14 S L2 (P) (UNSTABLE OR MASKED)  
 L4 5 DUPLICATE REMOVE L3 (9 DUPLICATES REMOVED)  
 L5 0 S (DIPEPTIDYL ALKYL KETONE)  
 L6 1 S (DIPEPTIDYL FLUOROALKYL KETONE) OR (DIPEPTIDYL CHLOROALKYL KE  
 L7 2933765 S ACETATE OR SUCCINATE OR TARTRATE OR FUMARATE OR PHOSPHATE OR  
 L8 0 S L7 (P) L4  
 L9 790513 S (METABOLIC DISORDER) OR DIABETES OR (IMPAIRED GLUCOSE TOLERAN  
 L10 1 S L4 (P) L9

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COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
95.04	95.25

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-2.60	-2.60

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